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KNOBBE MARTENS OLSON & BEAR LLP
620 NEWPORT CENTER DRIVE
SIXTEENTH FLOOR
NEWPORT BEACH, CA 92660

EXAMINER	
HUYNH, PHUONG N	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/847,208	Applicant(s) SAXON ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- Th MAILING DATE of this communication appears on the cov r she t with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,22-27,29,30,40-54 and 73-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 22-27, 29-30, 40-54, and 73-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-6, 22-27, 29-30, 40-54, and 73-76 are pending.

2. In view of the amendment filed 1/29/02, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-6, 22-27, 29-30, 40-52, 54 and 73-76 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) an isolated fusion molecule (SEQ ID NO: 7) consisting of a first polypeptide sequence (SEQ ID NO: 3) other than an antibody variable region, capable of specific binding to a native IgG inhibitory receptor wherein the inhibitory receptor contains an immune receptor tyrosine-base inhibitory motif (ITIM) that expressed on mast cells, basophils or B cells functionally connected to a second polypeptide sequence of SEQ ID NO: 6 other than an antibody variable region capable of specific binding directly to a native IgE receptor (FcεR) wherein the inhibitory receptor is a low-affinity IgG receptor FcγRIIb of human origin and said IgE receptor is FcεRI of human origin, (2) the said first and second polypeptide sequences are connected through a linker which is a polypeptide sequence consists of 5 to 25 amino acid residues as recited in claims 22-26 or said first and second polypeptide is fused to each other; (3) the said first polypeptide sequence consisting of at least part of the hinge region, the CH2 and CH3 domains or the hinge region, the CH2 and CH3 domains of the constant region of a native human IgG1 heavy chain (SEQ ID NO: 3) functionally connected to said second polypeptide sequence wherein the second polypeptide sequence consists of at least part of the CH2, CH3 and CH4 domains or the CH2, CH3 and CH4 domains of a native human IgE heavy chain constant region via a polypeptide linker wherein the linker is 5 to 25, 10 to 25, 15 to 25 amino acid residues; (4) the said fusion molecule is covalently linked to a second identical fusion to form a homodimer through one ore more disulfide bonds, **does not** reasonably provide enablement for (1) *any* isolated fusion molecule "comprising" *any* first polypeptide sequence, other than an antibody variable region capable of specific binding to any native IgG inhibitor receptor comprising an immune receptor tyrosine-based inhibitory motif (ITIM),

expressed on mast cells, basophils or B cells functionally connected to *any* second polypeptide sequence other than an antibody variable region capable of specific binding directly to any native IgE receptor (FcεR), (2) *any* isolated fusion molecule "comprising" *any* first polypeptide sequence wherein said first polypeptide comprises an amino acid sequence having at least 90% sequence identity with the hinge-CH2-CH3 portion of *any* IgG immunoglobulin heavy chain constant region selected from the group consisting of IgG2, IgG2, IgG3 and IgG4 functionally connected to *any* second polypeptide sequence other than an antibody variable region capable of specific binding directly to any native high-affinity IgE receptor FcεRI for preventing acute or chronic IgE mediated reaction to any allergen(s). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims for the same reasons set forth in Paper No 7.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one fusion molecule of SEQ ID NO: 7 consisting of a first polypeptide sequence (SEQ ID NO: 3) which contains a hinge, a CH2 and CH3 domains of the constant region of an IgG1 heavy chain (γhinge--CHγ2-CHγ-3) that binds to a native human low affinity FcγRIIb receptor fused to a second polypeptide of SEQ ID NO: 6 which contains a CH2, CH3 and CH4 domains of the constant region of an IgE heavy chain (CHε2-CHε3-CHε-4) that binds to a native high-affinity IgE receptor FcεRI (See page 24 lines 29-31 bridging page 25 line 1, example on page 53-54 of the specification). The specification further discloses said first polypeptide and said second polypeptide is linked through a 15 amino acids peptide linker and the resulting fusion molecule can connected to another fusion molecule by interchain disulfide bonds to form a homodimer or heterodimer with two different fusion molecules (See page 26, lines 5-14). The specification discloses the method of determining the % sequence identity between two amino acid sequences using the NCBI BLAST2.0 software wherein the parameters are set to

default and the penalty for mismatch at –1 (See page 14 lines 25 bridging page 15 lines 1-3). The specification defines on page 15 lines 25-30 that the "stringent" hybridization conditions as "may be hybridization in 50% formamide, 6x SSC, 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5x Denhardt's solution, sonicated salmon sperm DNA (100 μg/ml), 0.5% SDS and 10% dextran sulfate at 42 °C with washes at 42 °C in 2x SSC, and 0.1% SDS at 55C followed by a wash consisting of 0.2x SSC containing 0.1% SDS at 42 °C".

The specification fails to provide any guidance as how to make and use *any* isolated fusion molecule mentioned above for preventing acute or chronic IgE mediated reaction to any allergen(s) and treat autoimmune disorders. The transitional phrase "comprising" is open-ended. It expands the fusion molecule to include additional polypeptide in addition to the first and second polypeptides. Moreover, it expands the first polypeptide sequence to include additional amino acid residues at either end in addition to the polypeptide of SEQ ID NO: 3. Given the indefiniteness of the additional number of amino acids that may encompassed in the fusion molecule of the instant claims, it is unpredictable to determine which undisclosed fusion molecule will have the same structure and functions as SEQ ID NO: 7.

With regard to "amino acid sequence having at least 90% sequence identity", there is insufficient guidance as how to make and/or use *any* amino acid sequence having 90% identity with the hinge-CH2-CH3 portion of an IgG immunoglobulin heavy chain constant region or *any* amino acid sequence having 90% identity with SEQ ID NO: 3 or *any* amino acid sequence SEQ ID NO: 6 and still retain biological or immunological function such as inhibiting IgE mediated release of histamine *in vivo*. Although the method for determining the percent identity were mentioned on pages 14-15, the term "percent" is relative and can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Given the indefiniteness of the fusion molecule mentioned above, it is unpredictable as to assess which undisclosed fusion molecule comprises a first polypeptide and a second polypeptide each of which will have 90% identity to the claimed sequences of SEQ ID NOS: 3 and 6, respectively, and still retain functions. Furthermore, there is insufficient working examples in the specification as to any fusion molecule "comprising" a first polypeptide sequence "having at least 90% sequence identity" with the hinge-CH2-CH3 portion of an IgG immunoglobulin heavy chain constant region or SEQ ID NO: 3 functionally connected to a second polypeptide sequence "having at least 90% sequence identity" to native IgE receptor

(FcεR) will inhibit IgE mediated histamine release in vivo for treating allergic disease and autoimmune disorders.

It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495).

Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular). Since the specification fails to provide guidance regarding which amino acid within said "first polypeptide" and the "second polypeptide" can tolerate change, it follows that the fusion molecule comprising said first and second polypeptide is not enable.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

Applicants' arguments filed 1/29/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the fusion molecules themselves have a relatively simple structure and can be made by standard techniques, (2) it is well established a skill person with a PhD background in the art of recombinant DNA technology will be able to make the fusion molecule, (3) claim 1 contain and all depended claims contain the functional limitation that the IgG and IgE Fc domain (either native or variants) have the ability to bind to their respective surface receptors and the specification teaches which amino acids by way of examples are necessary for receptor binding as well as methods to determine the affinity of the Fc domain and thus the term "comprising" does not result in an indefinite number of fusion molecules with unpredictable activities, (4) the fusion molecules of the first and second polypeptides of the fusion protein can be joined using various linkers, may contain posttranslational modifications such as acetylation, glycosylation and prenylation, and the fusion molecules of the invention can also comprises multiple of the IgG and IgE Fc domains, for example, IgG-IgG-IgE or IgG-IgE-IgG Fc configuration and further comprising signal sequences for intracellular localization or extracellular export.

However, the fusion molecule comprising *any* first polypeptide other than the antibody variable region functionally connected *any* second polypeptide sequence. There is no **structure**

(SEQ ID) associated with function of any "first polypeptide" and any "second polypeptide" other than the fact that these polypeptides are not the antibody variable region. Further, the term "comprising" or "having" is open-ended. It expands the undisclosed fusion molecule to include additional amino acid at either or both ends, in addition to any amino acid sequence having only 90% sequence identity with the hinge-CH2CH3 portion of an IgG immunoglobulin. Given the indefinite number of undisclosed fusion molecule comprising indefinite number of undisclosed "first polypeptide" capable of binding to a native IgG functionally connected to indefinite number of undisclosed "second polypeptide", the specification as filed fails to enable even one skill in the art to practice the invention without undue amount of experimentation.

5. Claims 1-6, 22-27, 29-30, 40-52, 54 and 73-76 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the same reasons set forth in Paper No 7.

The specification does not reasonably provide a **written description** of (1) *any* isolated fusion molecule "comprising" *any* first polypeptide sequence, other than an antibody variable region capable of specific binding to any native IgG inhibitor receptor comprising an immune receptor tyrosine-based inhibitory motif (ITIM), expressed on mast cells, basophils or B cells functionally connected to *any* second polypeptide sequence other than an antibody variable region capable of specific binding directly to any native IgE receptor (FcεR), (2) *any* isolated fusion molecule "comprising" *any* first polypeptide sequence wherein said first polypeptide comprises an amino acid sequence having at least 90% sequence identity with the hinge-CH2-CH3 portion of *any* IgG immunoglobulin heavy chain constant region selected from the group consisting of IgG2, IgG2, IgG3 and IgG4 functionally connected to *any* second polypeptide sequence other than an antibody variable region capable of specific binding directly to any native high-affinity IgE receptor FcεRI for preventing acute or chronic IgE mediated reaction to any allergen(s).

With the exception of a fusion molecule encoding by SEQ ID NO: 7, there is insufficient written description about the structure associated with function of *any* fusion molecule mentioned above. Since only one fusion molecule (SEQ ID NO: 7) consisting of a first polypeptide of SEQ ID NO: 3 which encoded by SEQ ID NO: 1 functionally connected to a second polypeptide of

SEQ NO: 6 which encodes by SEQ ID NO: 4, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

With the exception of oligonucleotides of SEQ ID NOS: 174 and 175, there is no written description about the structure of any "nucleic acid" because by reciting hybridizing terminology in the claim, the nucleic acid can encompass an infinite number of nucleic acid that are capable of hybridizing under any conditions, including low stringency, to any undisclosed "nucleic acid molecule". Given the indefinite number of "nucleic acid" that may encompassed by the claims 40 and 41, the fusion molecule comprising a sequence encoded by the nucleic acid which hybridizes to any nucleic acid molecule "under stringent conditions" is not adequately described. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 1/29/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the fusion molecules themselves have a relatively simple structure and can be made by standard techniques, (2) it is well established a skill person with a PhD background in the art of recombinant DNA technology will be able to make the fusion molecule, (3) claim 1 contain and all depended claims contain the functional limitation that the IgG and IgE Fc domain (either native or variants) have the ability to bind to their respective surface receptors and the specification teaches which amino acids by way of examples are necessary for receptor binding as well as methods to determine the affinity of the Fc domain and thus the term "comprising" does not result in an indefinite number of fusion molecules with unpredictable activities, (4) the fusion molecules of the first and second polypeptides of the fusion protein can be joined using various linkers, may contain posttranslational modifications such as acetylation, glycosylation and prenylation, and the fusion molecules of the invention can also comprises multiple of the IgG and IgE Fc domains, for example, IgG-IgG-IgE or IgG-IgE-IgG Fc configuration and further comprising signal sequences for intracellular localization or extracellular export.

However, the fusion molecule comprising *any* first polypeptide other than the antibody variable region functionally connected *any* second polypeptide sequence. There is no **structure** (SEQ ID) associated with function of any "first polypeptide" and any "second polypeptide" other

than the fact that these polypeptides are not the antibody variable region. Further, the term "comprising" or "having" is open-ended. It expands the undisclosed fusion molecule to include additional amino acid at either or both ends, in addition to any amino acid sequence having only 90% sequence identity with the hinge-CH2CH3 portion of an IgG immunoglobulin. Given the indefinite number of undisclosed fusion molecule comprising indefinite number of undisclosed "first polypeptide" capable of binding to a native IgG functionally connected to indefinite number of undisclosed "second polypeptide", the specification as filed fails to enable even one skill in the art to practice the invention without undue amount of experimentation.

6. Claims 1-6, 22-27, 29-30 and 40-54 stand rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in Paper No 7. **This is a new matter rejection**.

Claims 1-6, 22-27, 29-30 and 40-54 as written represent a departure from the specification and the claims as originally filed because:

(1) The claims as originally filed require that an isolated fusion molecule comprising a first polypeptide sequence capable of specific binding to a native IgG inhibitory receptor comprising an immune receptor tyrosine-based inhibitory motif (ITIM), expressed on mast cells, basophils or B cells, functionally connected to a second polypeptide sequence capable of specific binding, directly or indirectly to a native IgE receptor (FcεR) and

(2) The specification does not have support for "other than an antibody variable region".

Applicants' arguments filed 1/29/02 have been fully considered but are not found persuasive.

Applicants' position is that it is the fusion molecules bind to two different types of immunoglobulins receptors, which are also referred as "Fc" receptors to reflect that they bind to the constant region and not the variable region of immunoglobulin. The language objected to was added merely to more clearly reflect this fact.

However, the specification and the claims as originally filed do not have support for "other than an antibody variable region". The specification on page 1 lines 17-19 discloses the constant region of the immunoglobulins.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-6, 27, 29-30, 40-43, 47-48 and 73-76 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,336,603 (Aug 1994, PTO 892) in view of Krauss *et al* (Eur J Immunol 25(1): 192-9, Jan 1995; PTO 892) and Basu *et al* (J boil Chem 268(18): 13118-27, June 1993; PTO 892) for the same reasons set forth in Paper No 7.

The '603 patent teaches a fusion molecule (CD4-IgG) comprising a first polypeptide sequence of human IgG1constant region (other than an antibody variable region) that is capable of binding to a native IgG receptor such as the FcγRIIb functionally connected to a second polypeptide sequence of CD4 (See column 3, Summary, in particular). The '603 patent further teaches the CD4 molecule is fused to the Fc portion of IgG1 wherein the Fc portion of IgG1 comprises at least the functionally active hinge, CH2 and CH3 domains of an immunoglobulin heavy chain which is at least 90% sequence identical with the human hinge-CH2-CH3 portion of an IgG immunoglobulin heavy chain constant region of SEQ ID NO: 3 (See column 5, lines 61-67, in particular). The '603 patent teaches additional fusion molecule such as IgE Fc receptor (See column 4, lines 19-20, in particular). The advantage of fusion molecule to IgG constant region is that it improves half-life of the molecule in plasma. Claim 40 is included in this rejection because the first polypeptide sequence is capable of specific binding to a native human FcγRIIb receptor, the nucleic acid that encodes said first polypeptide would hybridizes under stringent conditions to the complement of the hinge-CH2-CH3 coding sequence of SEQ ID NO:1.

The claimed invention as recited in claims 1-3, 6, and 47 differs from the reference only by the recitation of said fusion molecule comprises a second polypeptide sequence having at least 90% sequence identity with the amino acid sequence of SEQ ID NO: 6 and capable of binding to a native IgE receptor wherein said IgE receptor is a high-affinity FcεRI receptor or a low-affinity IgE receptor FcεRII (CD23), which can form a homodimer or heterodimer through one or more disulfide bonds (S-S) (See Fig 1, in particular).

The claimed invention in claims 73-76 differs from the references only by the recitation of said fusion molecule covalently linked to a second identical fusion molecule to form a homodimer wherein the linkage is through one or more disulfide bonds.

Krauss *et al* teach a recombinant CD4-IgE fusion molecule comprising a first polypeptide sequence of CD4 fused to the CH2-CH4 domains of the IgE heavy chain wherein the IgE CH2-CH4 polypeptide having at least 90% identity with SEQ ID NO: 6 that binds to the high affinity receptor (Fc epsilon RI) on basophils as well as low affinity receptor (Fc epsilon RII or CD23) on lymphoid cell (See abstract, Fig 1, in particular). Krauss *et al* further teach two identical fusion molecule such as CD4-IgE polypeptides can form homodimer by linking through one or more interchain disulfide bonds (See Fig 1, in particular).

Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains is sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE can block the release of histamine from cells expressing human Fc epison RI. Basu et al further teach the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains containing the Cys328 residue which can form interchain disulfide (S-S) bonds (See abstract, in particular). Claim 41 is included in this rejection because the second polypeptide sequence is capable of specific binding to a native human the high affinity receptor (Fc epsilon RI) on basophils as well as low affinity receptor (Fc epsilon RII or CD23), the nucleic acid that encodes said second polypeptide would hybridizes under stringent conditions to the complement of the CH2-CH3-CH4 coding sequence of SEQ ID NO: 4.

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the CD4 molecule as taught by the '603 patent with the human IgE molecule as taught by Krauss *et al* or Basu *et al* for a fusion molecule comprising the CH2-CH4 domains of the IgE heavy chain fused to the human Fc region of IgG comprising the hinge, CH2 and CH3 domains of an immunoglobulin heavy chain. It would have been obvious to one

having ordinary skill in the art at the time the invention was made to make homodimer by linking two identical fusion molecule through one or more interchain disulfide bonds as taught by Krauss *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to produce said fusion molecule because the '603 patent teaches fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular). Krauss *et al* teach the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains can bind to the high affinity receptor (Fc epsilon RI) on basophils as well as low affinity receptor (Fc epsilon RII or CD23) on lymphoid cell and Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains is sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE which can block the release of histamine from cells expressing human Fc epison RI.

Applicants' arguments filed 1/29/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the '603 patent teach fusion molecules comprising the CD4-Tcell receptor fused to the IgG constant domain, Krauss et al also teaches fusion molecules containing the CD receptor fused to IgE heavy chain constant domains and specifically Cε2, Cε3 and Cε4 and Basu et al teaches IgE Fc domain, (2) it is not obvious to replace the CD4 sequence with the IgE Fc sequence of Karuass or Basu et al, (3) these references described fusion molecule for the purpose of suppressing HIV proliferation, (4) there is no motivation to replace the CD4 sequences with any other sequences.

However, the '603 patent further teaches the CD4 molecule is fused to the Fc portion of IgG1 wherein the Fc portion of IgG1 comprises at least the functionally active hinge, CH2 and CH3 domains of an immunoglobulin heavy chain which is at least 90% sequence identical with the human hinge-CH2-CH3 portion of an IgG immunoglobulin heavy chain constant region of SEQ ID NO: 3 (See column 5, lines 61-67, in particular). The '603 patent teaches the advantage of fusion molecule to IgG constant region is that it improves half-life of the molecule in plasma. the '603 patent teaches fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular). Krauss *et al* teach the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains can bind to the high affinity

receptor (Fc epsilon RI) on basophils as well as low affinity receptor (Fc epsilon RII or CD23) on lymphoid cell and Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains is sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE which can block the release of histamine from cells expressing human Fc epison RI. The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

10. Claims 22-26 and 49-53 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,336,603 (Aug 1994, PTO 892) in view of Krauss *et al* (Eur J Immunol 25(1): 192-9, Jan 1995; PTO 892) and Basu *et al* (J boil Chem 268(18): 13118-27, June 1993; PTO 892) as applied to claims 1-6, 27, 29-30, 40-43 and 47-48 above and further in view of WO 88/09344 publication, PTO 1449) for the same reasons set forth in Paper No 7.

The teachings of the '603 patent, Krauss *et al* and Basu *et al* have been discussed supra.

The claimed invention in claims 22-26 and 49-53 differs from the references only by the recitation of said polypeptide linker is a polypeptide sequence consists of 5, 10 or 15 to 25 amino acid residues.

The WO 88/09344 publication teaches polypeptide linker wherein the polypeptide sequence is Gly-Gly-Gly-Gly-Ser which is at least 5 amino acid residues and can be link in tandem to form (Gly-Gly-Gly-Gly-Ser)3 which is at least 15 amino acid residues or (Gly4-Ser)5 which is at least 20 amino acid residues wherein the polypeptide linker is designed so as to exhibit little propensity for secondary structure and not to interfere with domain folding when connecting the V_H carboxy-and V_L amino-termini which is the variable heavy and light chain of the immunoglobulin (See page 52, 1st paragraph, in particular). Claim 53 is included in this rejection because the linker sequence is same as the ones that are taught by the WO 88/09344 publication as disclosed on page 52 line 24 of the specification.

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to link a first polypeptide sequence such as the human hinge-CH2-CH3 portion of an IgG immunoglobulin heavy chain constant region and a second polypeptide such as the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains via a

polypeptide linker wherein the polypeptide linker having a polypeptide sequence consisting of 5 to 25 amino acid residues as taught by the WO 88/01737.

One having ordinary skill in the art at the time the invention was made would have been motivated to use said polypeptide linker because the WO 88/01737 teaches that these polypeptide linkers are designed not to have the propensity for forming secondary structure and thus avoid interfering with domain folding of the immunoglobulin (See page 52, 1st paragraph, in particular).

Applicants' arguments filed 1/29/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the '603 patent teach fusion molecules comprising the CD4-Tcell receptor fused to the IgG constant domain, Krauss et al also teaches fusion molecules containing the CD receptor fused to IgE heavy chain constant domains and specifically Cε2, Cε3 and Cε4 and Basu et al teaches IgE Fc domain, (2) it is not obvious to replace the CD4 sequence with the IgE Fc sequence of Karuass or Basu et al, (3) these references described fusion molecule for the purpose of suppressing HIV proliferation, (4) there is no motivation to replace the CD4 sequences with any other sequences.

However, the '603 patent further teaches the CD4 molecule is fused to the Fc portion of IgG1 wherein the Fc portion of IgG1 comprises at least the functionally active hinge, CH2 and CH3 domains of an immunoglobulin heavy chain which is at least 90% sequence identical with the human hinge-CH2-CH3 portion of an IgG immunoglobulin heavy chain constant region of SEQ ID NO: 3 (See column 5, lines 61-67, in particular). The '603 patent teaches the advantage of fusion molecule to IgG constant region is that it improves half-life of the molecule in plasma. the '603 patent teaches fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular). Krauss *et al* teach the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains can bind to the high affinity receptor (Fc epsilon RI) on basophils as well as low affinity receptor (Fc epsilon RII or CD23) on lymphoid cell and Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains is sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE which can block the release of histamine from cells expressing human Fc epison RI. The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

11. Claim 30 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,336,603 (Aug 1994, PTO 892) in view of Krauss *et al* (Eur J Immunol 25(1): 192-9, Jan 1995; PTO 892) and Basu *et al* (J boil Chem 268(18): 13118-27, June 1993; PTO 892) as applied to claims 1-6, 27, 29-30, 40-43 and 47-48 above and further in view of US Pat No. 5,925,351 (Jul 1999, PTO 892) for the same reasons set forth in Paper No 7.

The teachings of the '603 patent, Krauss *et al* and Basu *et al* have been discussed supra.

The claimed invention in claim 30 differs from the references only by the recitation of said immunoglobulin is IgG2, IgG3 or IgG4 having at least 90% sequence identity with the hinge-CH2-CH3 portion of an IgG immunoglobulin heavy chain constant region.

The '351 patent teaches fusion molecule (LT-β-R-Fc) comprising a first polypeptide of LT-β-R functionally connected to the human Fc domains of various IgG such as IgG1, IgG2, IgG3 and IgG4 having at least 90% sequence identity with the hinge-CH2-CH3 portion of an IgG immunoglobulin heavy chain constant region and one can select a Fc domain based on the desirable secondary effector functions for the particular immune response such as Fc domain of IgG1 is advantageous to harm or kill LT-bearing target cell, or IgG4 Fc domain if it desirable for binding of fusion molecule without triggering the complement system (See column 12 lines 58-67 bridging column 13, lines 1-4, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the Fc domains of IgG1 as taught by the '603 patent with the Fc domains of various IgG such as IgG2, IgG3 or IgG4 as taught by the '351 patent for a fusion molecule comprising the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains as taught by Krauss *et al* or Basu *et al* functionally connected to the various Fc domains of IgG1, IgG2, IgG3 or IgG4 as taught by the '603 patent and the '351 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to produce said fusion molecule because the '603 patent teaches fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular). Krauss *et al* teach the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains can bind to the high affinity receptor (Fc epsilon RI) on basophils as well as low affinity receptor (Fc epsilon RII or CD23) on lymphoid cell and Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains is sufficient for

binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE which can block the release of histamine from cells expressing human Fc epison RI. The '351 patent teaches that one can select a Fc domain based on the desirable secondary effector functions for the particular immune response such as Fc domain of IgG1 is advantageous to harm or kill LT-bearing target cell, or IgG4 Fc domain if it desirable for binding of fusion molecule without triggering the complement system (See column 12 lines 58-67 bridging column 13, lines 1-4, in particular).

Applicants' arguments filed 1/29/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the '603 patent teach fusion molecules comprising the CD4-Tcell receptor fused to the IgG constant domain, Krauss et al also teaches fusion molecules containing the CD receptor fused to IgE heavy chain constant domains and specifically Cε2, Cε3 and Cε4 and Basu et al teaches IgE Fc domain, (2) it is not obvious to replace the CD4 sequence with the IgE Fc sequence of Karuass or Basu et al, (3) these references described fusion molecule for the purpose of suppressing HIV proliferation, (4) there is no motivation to replace the CD4 sequences with any other sequences.

However, the '603 patent further teaches the CD4 molecule is fused to the Fc portion of IgG1 wherein the Fc portion of IgG1 comprises at least the functionally active hinge, CH2 and CH3 domains of an immunoglobulin heavy chain which is at least 90% sequence identical with the human hinge-CH2-CH3 portion of an IgG immunoglobulin heavy chain constant region of SEQ ID NO: 3 (See column 5, lines 61-67, in particular). The '603 patent teaches the advantage of fusion molecule to IgG constant region is that it improves half-life of the molecule in plasma. the '603 patent teaches fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular). Krauss *et al* teach the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains can bind to the high affinity receptor (Fc epsilon RI) on basophils as well as low affinity receptor (Fc epsilon RII or CD23) on lymphoid cell and Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains is sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE which can block the release of histamine from cells expressing human Fc epison RI. The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to

achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

12. Claims 44-46 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,336,603 (Aug 1994, PTO 892) in view of Krauss *et al* (Eur J Immunol 25(1): 192-9, Jan 1995; PTO 892) and Basu *et al* (J boil Chem 268(18): 13118-27, June 1993; PTO 892) as applied to claims 1-6, 27, 29-30, 40-43 and 47-48 above and further in view of Stevenson *et al* (J Immunol 158(5): 2242-50, March 1997; PTO 892) for the same reasons set forth in Paper No 7.

The teachings of the '603 patent, Krauss *et al* and Basu *et al* have been discussed supra.

The claimed invention in claims 44-46 differs from the references only by the recitation of said first polypeptide sequence additionally comprises at least part of the hinge of a native human IgG1 constant region which consists of at least part of the hinge, CH2 and CH3 domains of a native human IgG1 heavy chain constant region, in the absence of a functional CH1 region.

Stevenson *et al* teach the presence of a second human Fc gamma 1 in a fusion molecule such as chimeric FabFc Abs molecule that enhances effector functions of the chimeric molecule (See abstract, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to add additional human IgG1 constant region which consists of at least part of the hinge, CH2 and CH3 domains of a native human IgG1 heavy chain constant region, in the absence of a functional CH1 region as taught by the '905 patent for a fusion molecule comprising a first polypeptide consisting of more than one human IgG1 constant region as taught by Stevenson *et al* and a second polypeptide capable of binding to IgE receptor (FcεR) as taught by Krauss *et al* or Basu *et al.*

One having ordinary skill in the art at the time the invention was made would have been motivated to add additional part of the hinge, CH2 and CH3 domains of a human IgG1 heavy chain constant region to a fusion molecule because Stevenson *et al* teach the presence of a second human Fc gamma 1 in a fusion molecule such as chimeric FabFc can enhance effector functions of the chimeric molecule (See abstract, in particular). The '603 patent teaches fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular). Krauss *et al* teach the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains can bind to the high affinity receptor (Fc epsilon RI) on basophils as well as low affinity receptor (Fc epsilon RII or CD23) on lymphoid cell and Basu *et al* teach that

the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains is sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE which can block the release of histamine from cells expressing human Fc epison RI. The '351 patent teaches that one can select a Fc domain based on the desirable secondary effector functions for the particular immune response such as Fc domain of IgG1 is advantageous to harm or kill LT-bearing target cell, or IgG4 Fc domain if it desirable for binding of fusion molecule without triggering the complement system (See column 12 lines 58-67 bridging column 13, lines 1-4, in particular).

Applicants' arguments filed 1/29/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the '603 patent teach fusion molecules comprising the CD4-Tcell receptor fused to the IgG constant domain, Krauss et al also teaches fusion molecules containing the CD receptor fused to IgE heavy chain constant domains and specifically Cε2, Cε3 and Cε4 and Basu et al teaches IgE Fc domain, (2) it is not obvious to replace the CD4 sequence with the IgE Fc sequence of Karuass or Basu et al, (3) these references described fusion molecule for the purpose of suppressing HIV proliferation, (4) there is no motivation to replace the CD4 sequences with any other sequences.

However, the '603 patent further teaches the CD4 molecule is fused to the Fc portion of IgG1 wherein the Fc portion of IgG1 comprises at least the functionally active hinge, CH2 and CH3 domains of an immunoglobulin heavy chain which is at least 90% sequence identical with the human hinge-CH2-CH3 portion of an IgG immunoglobulin heavy chain constant region of SEQ ID NO: 3 (See column 5, lines 61-67, in particular). The '603 patent teaches the advantage of fusion molecule to IgG constant region is that it improves half-life of the molecule in plasma. the '603 patent teaches fusion protein comprising the IgG constant region improves half-life of the molecule in vivo (See column 7, line 65-67, in particular). Krauss *et al* teach the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains can bind to the high affinity receptor (Fc epsilon RI) on basophils as well as low affinity receptor (Fc epsilon RII or CD23) on lymphoid cell and Basu *et al* teach that the Fc region of IgE comprising C epsilon 2, C epsilon 3 and C epsilon 4 domains is sufficient for binding to the alpha chain of the high affinity IgE receptor with high affinity similar to native IgE and the Fc region of IgE which can block the release of histamine from cells expressing human Fc epison RI. The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to

achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

13. No claim is allowed.

14. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
July 1, 2002

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600